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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/458,610	12/10/1999	ELIZABETH G. NABEL	8642/88	9076

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BRINKS HOFER GILSON & LIONE
P.O. BOX 10395
CHICAGO, IL 60611

EXAMINER
WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/458,610	Nabel
Examiner	**Art Unit**
Anne Marie Wehbé	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *8/13/02 and 9/9/02* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213. .

Disposition of Claims

4) ☒ Claim(s) *106-142* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *106-142* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The request filed on 8/13/02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/458,610 is acceptable and a CPA has been established. Applicant's amendment received on 9/9/02 has also been entered. Claims 106-142 are pending in the instant application. An action on the CPA follows.

Those sections of Title 35, US code, not included in this action can be found in the previous office action, paper no. 11.

Claim Rejections - 35 USC § 112

The rejection of claims 106-142 under 35 U.S.C. 112, first paragraph, for lack of enablement is maintained. Applicant's amendments to the claims have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record discussed in detail below. Please note that while applicant's amendment received on 9/9/02 requested the amendment of claims 106-108, 115, and 120, the applicant has not provided any arguments in response to the pending rejections of the claims.

The amendments to claims 106-108 and 115 to recite a "transformed" rather than a "transfected" vascular cell, and/or the amendments to the claims to recite the use of syngeneic

cells have already been indicated as enabled by the instant specification, see the interview summary of 7/11/02, paper no. 17. The amendment of claim 120 to recite "wherein the protein is the gene product of a marker gene" is directed to the rejection of claim 120 under 35 U.S.C. 112, second paragraph. Thus, the amendments to the claims do not address the instant grounds for lack of enablement which involved the lack of enablement for the treatment of any condition or disease by the site-specific installation of any type of autologous or syngeneic vascular cells, endothelial cell, smooth muscle cell, or parenchymal cell, transformed or untransformed, in any mammal.

Please note that in the interview between the examiner of record, the applicant, and applicant's representative on 7/11/02, paper no. 17, the examiner noted that claims 106-108 would be considered allowable if the applicant provided an alternative use for the methods of introducing a protein in a mammal other than the treatment of disease. The applicant has not made of record any alternative use for the claimed methods.

Since the applicant has not provided any arguments regarding this rejection, the rejection of record stands. For the sake of clarity in prosecution, the grounds for rejection of claims 106-142 under 35 U.S.C. 112, first paragraph, as presented in the previous office action, are reiterated below.

In regards to the failure of the specification to provide an enabling disclosure for the treatment of any condition or disease by the site-specific installation of any type of autologous or syngeneic vascular cells, endothelial cell, smooth muscle cell, or parenchymal cell, transfected or untransfected, in any mammal, the applicant has previously argued that the specification provides

sufficient guidance for methods of delivery of transfected cells to blood vessels in a mammal, for example by the use of a catheter, and further suggests the treatment of cardiovascular disease using transfected cells which therapeutic proteins, such disclosed on page 27 of the specification. The applicant has also argued that , "... the skilled artisan would appreciate that the presence of a therapeutic protein in the vicinity of where such a protein might have its therapeutic effect , would results in treatment of the disease..." (applicant's arguments, page 9).

While the specification is primarily directed to the administration of **transformed** endothelial cells to blood vessels *in vivo* for the treatment of cardiovascular conditions, the claims broadly read on the administration of **untransformed** vascular cells or endothelial cells for the treatment of disease. The specification does not provide guidance for the administration of non-transformed cells or teach types of non-transformed cells which naturally secrete therapeutic levels of any protein such that the administration of the non-transfected cells results in the treatment of any disease or condition including cardiovascular disease. In regards to the delivery of cells transfected with a putative therapeutic gene, the specification's working examples demonstrate the transfection of endothelial cells with a vector encoding lac-Z, and the installation of these cells by balloon catheter to blood vessels *in vivo*. The specification reports that the endothelial cells expressed detectable levels of β-galactosidase following transplantation. The specification also states that expression could be detected for approximately six weeks. However, the specification does not correlate the level of β-galactosidase with any therapeutic effect on any disease symptom or teach that the expression of similar levels of any other protein, such as FGF

or tPA, for similar periods of time would result in any effect on any cardiovascular condition such as atherosclerosis, restenosis, or heart disease. The specification also fails to provide evidence that the delivery of any other type of transfected cell to any other cellular location using any method of delivery would result in the expression of therapeutic levels of protein or the treatment of any disease or condition. Furthermore, the references cited in the previous office action, Verma et al., Ledley et al., and Orkin et al., teach the unpredictability of achieving therapeutic levels of expression of a transgene in vivo by either direct or indirect administration of a recombinant vector or cells transduced/transfected with a recombinant vector. Thus, contrary to applicants assertion, the skilled artisan would not predict that the expression of any level of a putative therapeutic protein "in the vicinity" of diseased tissue or cells would result in a therapeutic effect on the disease to be treated.

Case law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves. *In re Gardner* 166 USPQ 138 (CCPA) 1970. The office has analyzed the specification in direct accordance to the factors outlined in In re Wands, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of working examples, and presented detailed scientific reasons supported by publications from the prior art for the finding of a lack of enablement in the instant. It is also noted that case law including the Marzocchi decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see *In*

re Marzocchi 169 USPQ 367, and *Ex parte Sudilovsky* 21 USPQ2d 1702). Further, the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). Thus, in view of the art recognized unpredictability of achieving therapeutic levels of gene expression *in vivo* using transfected cells at the time of filing, the lack of guidance concerning the level and duration of gene expression of any gene from any transfected cell at any cellular location *in vivo* which correlates with any therapeutic effect on any disease or condition, the absence of working examples which demonstrate the expression of therapeutic levels of gene expression *in vivo* by transfected cells, and the breadth of the claims, it would have required undue experimentation to practice the instant invention as claimed.

The rejection of claim 120 under 35 U.S.C. 112, second paragraph, for indefiniteness is withdrawn in view of applicant's amendment to claim 120.

No claims are allowed.

This is a CPA of applicant's earlier Application No. 09/458,610. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, THIS ACTION IS MADE FINAL even though it is a first action in this

case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER